Fluorine Chemistry



Oh, Kitty, how nice it would be if we could only get through into Fluoro-Carbon Chemistry! I'm sure it's got, oh! such beautiful things in it!

Fluoro Natural Products



D. O'Hagan, D. B. Harper J. Fluorine Chem. 1999, 100, 127.

Fluoro Medicine



9-Fluorohydrocortisone acetate





Properties of Fluorine Atom

	IP	EA	vdW radius	EN	BE CH ₃ -X	CH ₃ -X
	(kcal/mol)	(kcal/mo	l)(Pauling)(Å)(l	Pauling	g)(kcal/mol)	(Å)
н	313.6	17.7	1.20	2.1	99	1.09
F	401.8	79.5	1.35	4.0	116	1.39
CI	299.0	83.3	1.80	3.0	81	1.77
O (OH)	310.4	33.7	1.40	3.5	86	1.43

IP=Ionization potential, EA=Electron affinity, EN=Electronegativity, BE=Bond energy.

Rotational Barrier of CF₃





 $\begin{array}{ll} \mathsf{R} = {}^{i}\!\mathsf{Pr} \ , \ \Delta\mathsf{G}^{\ddagger} \bullet = 14.0 \ \text{kcal/mol} \\ \mathsf{R} = \mathsf{CF}_{3} \ , \ \Delta\mathsf{G}^{\ddagger} = 14.5 \ \text{kcal/mol} \\ \end{array} \qquad \begin{array}{ll} \mathsf{R} = {}^{i}\!\mathsf{Pr} \ , \ \Delta\mathsf{G}^{\ddagger} = 109.8 \ \text{kcal/mol} \\ \mathsf{R} = \mathsf{CF}_{3} \ , \ \Delta\mathsf{G}^{\ddagger} = 109.2 \ \text{kcal/mol} \\ \end{array}$

Electonic Effect of Fluorine



Electronic Effect of CF₃



negative hyperconjugation in aromatic ring

syn-Clinal Effect



Stereoselectivity by M-F Interaction



Hydrogen Bonding



M-F Interaction

Metal	Li	Na	Κ	Cs	
M-F (Å) ^a	2.23~2.29	2.15~2.91	2.67~3.39	2.87~3.61	
rF+rM (Å) ^b	2.92	3.26	3.70	4.07	
∆: (M-F)-(rF+rM) (Å)	-0.66	-0.73	-0.67	-0.83	
∆ / (rF+rM) (%)	-22.6	-22.4	-18.1	-20.4	
	AI	Ti	Zr	Hf	
	1.77~1.81	2.03~2.10	1.94~2.18	2.31~2.38	
	2.78	2.82	2.95	2.94	
	-0.99	-0.76	-0.89	-0.60	
	-35.6	-27.0	-30.2	-20.4	
	Sn	Zn	Pd	Ag	
	2.05~2.46	2.80	3.13~3.16	2.64~2.72	
	2.93	2.72	2.72	2.79	
	-0.68	+0.08	+0.43	-0.11	
	-23.2	+2.9	+15.8	-3.9	

^aDetermined by X-ray crystal structure analysis ^bSum of vdW radii of M and F

Stereoselectivity by M-F Interaction



M-F Interaction in -F Enolate



syn



anti

Μ	∆E(<i>anti-syn</i>) (kcal/mol)	M-F(<i>syn</i>) (Å)
-	1.8	-
Li	13.2	1.86
Na	13.6	2.21
К	10.8	2.62



Itoh, Y.; Yamanaka, M.; Mikami, K. J. Am. Chem. Soc. 2004, 126, 13174-131



Effect of Fluorine

Mimic Effect



Hydrolysis of oxetan acetal



Stable Analog of TXA₂



X = H TXA₂ t_{1/2} = 30 sec (pH 7.3, 23 °C) X = F 10,10-F₂-TXA₂



COX Pathway of Arachidonic Acid Metabolism



Prostacyclin and Stable Analogs



FBC: Fluorous Biphasic Catalysis



Strategies and Properties in Fluorous Liquid/Liquid System

- 1. Catalyst recycle by simple phase separation
- 2. Single phase by moderate heating
- 3. Extremely low polarity and viscosity

ate transition metal catalyzed hydroformylation in FBC



Rh cat. = RhH(CO){P(CH₂CH₂C₆F₁₃)₃}

Horvath, I. T.; Rabai, J. Science 1994, 266, 72.

ewis acid-catalyzed Friedel-Crafts reaction in FBC



Concept of Micro Reactor



Properties & Effects

- Very small volume (μ l order) -> Easy control of temparature
- Laminar flow condition -> Efficiency for heterogeneous catalysi
- Diffusional mixing -> Shorter reaction time

Fluorinating Reagent

Electrophilic



Nucleophilic

HF, HF/P y (Olah reagent), SF₄, Et₂NSF₃(DAST), MF(M=Cs, Rb, K, Na, Li), $Bu_4NF(TBAF)$, Et₂NCF₂CHCIF(Yarovenko reagent), Et₂NCF₂CHFCF₃(PPDA)

Perfluoroalkylating Reagent

Electrophilic



Nucleophilic

R_fLi、R_fCu、R_fZn、CF₃SiMe₃

Enantioselective Fluorinating Reagent







Enantioselective Fluorination (II)



Enantioselective Fluorination (III)



Plausible Transition State of Enantioselective Fluorination



almost prependicular to the benzene ring

Enantioselective Fluorination by Selectfluor in Conbination with Cinchona Alkaloids

Selectfluor







DHQB

DHQDA

Enantioselective Fluorination with Cinchona Alkaloids



Enantioselective Fluorination with Cinchona Alkaloids (II)



a) The reaction was carried out in MeCN at -20°C.

N-Fluoro Ammonium Salts of Cinchona Alkaloids



Enantioselective Fluorination with Fluorinated Cinchona Aklaloids



R	Temp(°C)	yield(%)	ee(%)
Me	-40	98	50
	-60	80	56
Bn	-40	96	42

Enantioselective Fluorination with Fluorinated Cinchona Alkaloids (II)



56% yield, 94%ee

Enantioselective Fluorination with Phase Transfer Catalyst



92% yield, 69%ee



Catalytic Enantioselective Fluorination by Chiral Lewis Acid





85-95% yield, 90%ee


Enantioselective Nucleophilic Fluorination

Kinetic resolution by chiral DAST derivative



Kinetic resolution by chiral phosphonium fluoride



Diastereoselective Perfluoroalkylation with Zinc



Diastereoselective Perfluoroalkylation to Li Enolate



Fluoride Elimination



Enantioselective Electrophilic Trifluoromethylation



Enantioselective Nucleophilic Trifluoromethylation

R	cat. (mol%)	Time(h)	yield(%)	ee(%)
Н	10	2	>99	37
Me	20	2	91	48
<i>i</i> -Pr	20	8	87	51

Diastereoselective Nucleophilic Perfluoroalkylation

L L Cr (CO) ₃	<респорт Напрания и на селото н На селото на селото на На селото на селото н На селото на	R _f Li Ether / -40 °C		R H
R	R _f Li	Time(h)	yield(%)	de(%)
Ме	C ₂ F ₅ Li	1	88	88
	<i>i</i> -C ₃ F ₇ Li	12	76	76
OMe	C ₂ F ₅ Li	1	100	100

Hydrogenation of Monofluoro Olefin

Hydrogenation of Trifluoromethyl Olefin

Reduction of Aromatic Ketone

Х	R	H ₂ (atm)	S/C ^a	time (h)	% yield	<u>% ee</u>
Н	CF_3	10	11000	16	100	96
CI	CF_3	8	2000	4	100	94
OMe	CF_3	8	2000	4	100	96
Н	Me	8	100000	60	97	99
CI	Me	8	20000	16	99.9	99
OMe	Me	10	20000	1	100	100

^aSubstrate/Catalyst molar ratio

Reduction of Aliphatic Ketone

Reduction of -Ketoester

Reduction of imino ester

^aPd(OCOCH₃)₂ was used and the reaction temprature was 35 °C. ^bCF₃C(OEt)(NHPMP)CO₂Et was obtained in 60% yield. ^c5 eq. of *n*-BuNHSO₄ was added.

Hydroboration

Effect of Trifluoromethyl Group in Hydroboration

Dihydroxylation

 $\begin{array}{c|c} H_{II,I} & LUMO (eV) & Charge of carbonyl carbon \\ X_3C & & & +0.61 \\ X = CI & -4.88 & +0.64 \end{array}$

Plausible Mechanism of Ene or Friedel-Crafts Reaction

Carbonyl-Ene Reaction of Methyl Substituted Olefin

Carbonyl-Ene Reaction with Hemiacetal

Carbonyl-Ene reaction Catalyzed by Cationic Pd Catalyst

Non Catalyzed Aldol Reaction with Fluoral

Aldol Reaction with Fluoral

Aldol Reaction of Methyl Substituted Si Enolate with Fluoral

Aldol Reaction of Fluorine Substituted Si Enolate

Friedel-Crafts Reaction of Silyl Enol Ether

^aThe enantiomeric excess of (Z)-11. ^bThe usual aldol product was obtained as the TMS ether. The diastereomeric ratio=1:4.

Plausible Mechanism of F-C Reaction of Silyl Enol Ether

Application of the Silyl Enol Ether F-C Product

Industrial Application of the Silyl Enol Ether F-C Product

F-C Reaction of Vinyl Ether

20mol %

Η

4'-Me-Ph

64 % (5:1) 85

Application of the Vinyl Ether F-C Product

F-C Reaction of Aromatic Compounds

R	cat. (mol %) additive (mol %)	% yield	p-1:o-1	% ee ^a
Me	30	-	82	4:1	73
Me	5	-	94	4:1	84
<i>п</i> -Ви	15	-	85	8:1	83
Ph	10	-	90	3:1	54
Me	10	(R)-6,6'-Br ₂ -BINOL (10)) 89	4:1	90
<i>п</i> -Ви	10	(R)-6,6'-Br ₂ -BINOL (10)) 90	8 : 1	90

^aThe enantiomeric excess of *p*-1.

F-C Reaction Catalyzed by Cu-BOX

F-C Reaction Catalyzed by Cu-BOX (II)

F-C Reaction Catalyzed by Cu-BOX (III)

F-C Reaction Catalyzed by Cationic Pd Complex

Enantioselective Addition of Dialkyl Zinc



Enantioselective Alkylation to -F Ketone



PTC

Cyclopropanation of Fluoro Olefin



Hydrogen Bonding in Cyclopropanation Product Derivative



Fluorine Chemistry



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